EXHIBIT C

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HAND DELIVERY

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Food and Drug Administration
Department of Health and Human Services
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12420 Parklawn Dr.
Rockville, MD 20857

CITIZEN PETITION

The Washington Legal Foundation (WLF) hereby submits this petition under 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drug withdraw the "Draft Policy Statement on Industry-Supported Scientific and Educational Activities," dated November 19, 1992. Petitioner further requests that FDA formally adopt a policy that recognizes the important role played by off-label uses of approved drugs and medical devices in the proper administration of health care in this country. That policy should state that while drug and medical device manufacturers should not label their products for unapproved uses, they will not be the subject of compliance action for facilitating efforts by health care professionals to disseminate truthful information about off-label uses of those products. The policy should also state that FDA will not interfere with the First Amendment rights of doctors and their patients to receive such information. A proposed policy statement is attached hereto as Exhibit H.

EXHIBIT C

FDA's conduct in recent years suggests that FDA has a strong aversion to the dissemination of information regarding off-label uses of drugs and medical devices; that in its "perfect world" FDA would prohibit all such information flow. Petitioner believes, to the contrary, that off-label uses of approved drugs and medical devices serve an invaluable function in delivering quality health care and (when administered under the direction of health care professionals) can offer therapeutic advantages not available when limited to FDA-approved labeling.

Furthermore, manufacturers should not be subject to sanction simply because, in furtherance of their economic self-interest, they assist in the dissemination of truthful information regarding unapproved uses for their products. FDA is authorized, of course, to prevent manufacturers from misbranding their products by including unapproved uses on product labels; but FDA has stretched its "labeling" authority far beyond anything contemplated by Congress in adopting the Federal Food, Drug, and Cosmetic Act (the "FDC Act"), 21 U.S.C. §§ 301 et seq. Congress did not contemplate, for example, that FDA would attempt to prevent drug manufacturers from distributing to doctors copies of recognized medical textbooks; yet FDA has done just that, without so much as raising a question regarding the accuracy of any information contained in those textbooks.

A. ACTION REQUESTED

FDA published its "Draft Policy on Industry-Supported Scientific and Educational Activities" (the "Draft Policy") in the

Federal Register on November 27, 1993. See 57 Fed. Reg. 56412 (attached hereto as Exhibit A). Petitioner requests (as it previously did in response to FDA's request for comments on the Draft Policy) that FDA not adopt the Draft Policy in final form. Moreover, since the Draft Policy has the effect of chilling speech that is protected by the First Amendment and is outside the purview of FDA's jurisdiction, Petitioner further requests that FDA formally withdraw its Draft Policy and refrain from taking any enforcement action based on the policy or the concepts embodied in the policy.

Petitioner further requests that FDA formally adopt a policy that recognizes the important role played by off-label uses of approved drugs and medical devices in the proper administration of health care in this country, and that declares that FDA will not interfere in non-labeling activities of drug and medical device manufacturers whose effect is to promote -- through the dissemination of truthful medical information -- off-label uses of approved drugs and medical devices.

B. INTERESTS OF PETITIONERS

WLF is a public interest law and policy center with more than 100,000 members and supporters nationwide. It devotes a substantial portion of its resources to defending the rights of individuals and businesses to go about their affairs without undue interference from government regulators. Among WLF's members are doctors and medical patient who wish to receive information about off-label uses of FDA-approved drugs and medical devices, as well

as medical patients who wish their doctors to receive such information.

C. STATEMENT OF GROUNDS

Congress adopted the FDC Act in 1938 to regulate the sale of manufactured drugs to the general public; it later amended the FDC Act to require that medical devices be cleared by FDA before commercial sale. Section 505(a) of the FDC Act, 21 U.S.C. § 355(a), provides that no "new drugs" may be introduced into interstate commerce unless they undergo testing and are approved as safe by FDA. Section 520 of the FDC Act, 21 U.S.C. § 360j, imposes similar restrictions on medical devices.

Once FDA has approved a drug or medical device for introduction into interstate commerce, its statutory authority to control dissemination of information regarding the product is rather limited. Section 502 of the FDC Act, 21 U.S.C. § 352, defines as "misbranded" any FDA-approved drug or medical device that does not bear an FDA-approved label which specifies the uses for which FDA has approved the drug or device, and "adulteration" or "misbranding" of any drug or medical device in interstate commerce is prohibited under §§ 301 (b) and (c) of the FDC Act, 21 U.S.C. §§ 331(b) and (c). But the FDC Act does not grant FDA authority to control what those other than the manufacturer say about the proper uses of FDA-approved drugs and medical devices.

Petitioner recognizes that FDA is authorized to restrict what manufacturers have to say about their drugs and medical devices to the extent that such speech constitutes "labeling" of those

products within the meaning of § 201(m) of the FDC Act, 21 U.S.C. § 321(m).[1] Petitioner believes, however, that in its zeal to prevent manufacturer support for dissemination of any information regarding off-label uses of their products, FDA has far exceeded its statutory "labeling" authority -- as well as trammeling the First Amendment rights of both providers and recipients of that information.

Those Affected by FDA Policy. Numerous health care providers and patients have a vital interest in the free-flow of information regarding off-label uses of FDA-approved drugs and medical devices. This Petition will attempt to highlight the interests of just a few of those individuals.

Oncology, the study and treatment of cancer in humans, is a medical specialty in which off-label uses of approved drugs is particularly prevalent. That is so because drugs approved by FDA for treating one form of cancer in adults often have been found to be safe and effective (at different dosage levels) for treating the same form of cancer in children and for treating other forms of cancer. In addition, physicians routinely use oncology agents in combinations that are not referenced in the FDA-approved labeling. Yet, due to the tremendous expense of conducting the clinical trials necessary to obtain FDA approval for those other uses, drug

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[1] FDA's regulatory authority also extends to the regulation of "advertisements" for prescription drugs (21 U.S.C. § 352(n)) and for restricted devices, i.e., hearing aids (21 U.S.C. § 352(q)). Section 352(n) requires that advertisements for prescription drugs include such information -- regarding side effects, contraindications, and effectiveness -- as FDA may prescribe by regulation.

companies often determine that such expenditures are economically unjustified. Even when separate approval is sought, it takes years to conduct the requisite clinical studies and obtain FDA approval to change the product labeling. As a result, a significant percentage of treatment of cancer patients in this country consists of off-label uses of approved drugs (i.e., use of such drugs for uses other than, or in a manner other than, those approved by FDA). Virtually all oncologists believe that the public interest is best served by permitting the widest possible dissemination of accurate information about off-label uses of approved drugs; without such information, oncologists are not in a position to provide their patients with the best possible medical care.

Orthopedic physicians are another group with a strong interest in the free-flow of information about off-label uses of FDA-approved drugs and medical devices. A medical device commonly used by orthopedists is a bone screw, which is used to treat certain spinal conditions, in affixing spinal rods or plates by attachment to vertebral pedicles. FDA has estimated that physicians perform 50,000 to 70,000 pedicle fixation procedures annually; for some of those applications, pedicle screws have been shown to be the best therapeutic alternative. No company, however, has obtained FDA permission to label its device a "pedicle screw." Most orthopedists believe that the public interest is best served by permitting the widest possible dissemination of accurate information about FDA-approved medical devices such as bone screws;

without such information, orthopedists are not in a position to provide their patients with the best possible medical care.

Statutory Violations. Section 201(m) of the FDC Act defines "labeling" as "all labels and other written, printed, or graphic matters (1) upon any article or any of its containers or wrappers, or (2) accompanying such article."[2] FDA regulations intended to implement the agency's labeling authority (21 C.F.R. Part 201) and its device labeling authority (21 C.F.R. Part 801) do not attempt to expand upon the statutory definition of "labeling." In light of that statutory definition, Petitioners are at a loss to understand recent efforts by FDA to brand as unauthorized "labeling" certain manufacturer activity that does not fit within any commonly understood definition of that term.

For example, FDA recently disapproved efforts by a major pharmaceutical company to distribute to physicians (free of charge) a standard medical textbook: DeVita, Hellman, and Rosenberg (eds.), Selected Readings from Principles & Practices of Oncology (J. B. Lippincott Co., 3rd ed. 1989). See Exhibits B and C.[3] The textbooks were to be distributed at a meeting of the American Society of Clinical Oncology. Although the textbooks discussed off-label uses of the pharmaceutical company's products, the books

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[2] The FDC Act further defines a "label" as "a display of written, printed, or graphic matter upon the immediate container of any article. . ." FDC Act § 201(k), 21 U.S.C. § 321(k).

[3] Exhibits B and C have been redacted to remove all references to the pharmaceutical company in question. Petitioners assume, however, that FDA can verify the authenticity of these documents from its own files.

were not "accompanying" any of those products; indeed, none of the company's products were available at the meeting. While Kordel v. United States, 335 U.S. 345 (1948), held that the word "accompanying" as used in § 321(m) is to be defined broadly, Kordel still required that there be some substantial relationship between a product and the written matter alleged to constitute "labeling" for that product. Accordingly, FDA's claim that distribution of the textbooks constituted "labeling" is clearly at odds with 21 U.S.C. § 321(m)'s definition of that term.[4]

FDA's November 1992 "Draft Policy" does further violence to the statutory definition of "labeling." The Draft Policy in effect treats all corporate-sponsored scientific and educational programs as "labeling," and then establishes "safe harbors" within which a company is not likely to face enforcement action.[5] That definition is totally at odds with the statutory definition of "labeling":

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[4] FDA Compliance Policy Guide (CPG) 7153.13 (Rev. 8/31/89), entitled "Seizure of Books that Constitute Misleading Labeling" (Exhibit D), concedes that printed material does not constitute "labeling" unless it actually accompanies the drug or medical device that it purports to label. However, CPG 7153.13 provides little useful direction regarding FDA's interpretation of "accompany"; the CPG states opaquely and ungrammatically, "Although all accompanying materials constitute labeling, the extent to which they 'accompany' it may be direct or indirect."

[5] We do not understand FDA to be attempting to base its Draft Policy on its statutory authority to regulate prescription drug advertising under 21 U.S.C. § 352(n). For one thing, the Draft Policy purports to cover all therapeutic and diagnostic products (human and animal drugs, biological products, and medical devices), not simply prescription drugs. Moreover, the definition of "advertisement" apparently contemplated by § 352(n) could not easily be stretched to cover industry-supported scientific and educational activities; indeed, § 352(n) appears to limit the term "advertisement" to written materials only.

"all labels and other written, printed, or graphic matters (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C. § 321(m). Oral speeches given at scientific and educational programs cannot be termed "labeling" because they are not "labels and other written, printed, or graphic matters."

Moreover, FDA certainly cannot claim that discussions among scientists and medical professionals regarding their findings relating to non-FDA-approved uses of a drug or medical device intrinsically constitute "labeling" for the product in question. Indeed, the free flow of information is vital to the advancement of medical science and patient welfare. That being the case, we fail to see how such discussions are converted to "labeling" the moment that a manufacturer supplies financial support for the forum at which such discussions take place. Furthermore, there is no statutory support for the Draft Guidelines' attempt to impose a taint on the statements of <u>everyone</u> who speaks at a scientific or educational program simply because FDA has deemed the program itself to be insufficiently independent of a financial backer. A speaker at such a program without any ties to a manufacturer cannot be deemed to be speaking on behalf of the manufacturer (such that FDA would consider his or her statements to constitute "labeling") simply because he or she recommends off-label uses of the company's product.

While Petitioner finds the Draft Policy highly objectionable and request that it be withdrawn, Petitioner is even more concerned

by a series of Warning Letters that FDA issued in August 1993. The Warning Letters indicate that FDA is not even willing to abide by the "safe harbor" provisions contained in its own Draft Policy. The letters all concerned medical educational programs held earlier this year in Florida and St. Louis entitled, "Pedicle Fixation of the Lumbar Spine and other Advanced Techniques." Although many FDA-cleared devices are being used in pedicle fixation procedures, FDA has not approved their use for pedicle fixation. Thus, the Florida and St. Louis educational programs focused on an off-label use. FDA has given no indication that it believes that the programs failed to come within the Draft Policy's "safe harbor" for "independent" educational activities. Nonetheless, FDA stated in its Warning Letters (sent to seven of the numerous pedicle screw manufacturers who participated in the programs) that participation in the programs constituted "misbranding" of the medical devices and "adulterated" each manufacturer's entire stock of pedicle screws.[6]

What terrible misdeeds had the pedicle screw manufacturers committed to warrant their receipt of company-threatening warning letters? In general, FDA alleged that: (1) the manufacturers supplied samples of their product for use during training sessions at the programs; (2) the manufacturers provided information

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[6] The Warning Letters gave each manufacturer 15 days to correct its violation. Failure to do so would have risked closure of the manufacturer's business and seizure of its entire stock of medical devices, plus civil penalties. A copy of one of the pedicle screw warning letters is attached hereto as Exhibit E.

regarding their product; and/or (3) doctors affiliated with the manufacturers participated in demonstrations of spinal fixation of pedicle screws. In the absence of any FDA allegation that the Florida and St. Louis programs were not "independent" of manufacturer control or that the products of one manufacturer were favored over those of other manufacturers, the manufacturers appear to have been in full compliance with FDA's Draft Policy.[7]

FDA's decision to send out Warning Letters despite a lack of evidence of noncompliance with the Draft Policy is another strong indication that FDA's principal motivation is to eliminate all off-label use of approved drugs and medical devices, or at least the dissemination of information about off-label use. As Petitioner has noted, off-label use of approved drugs and devices is not an evil to be tolerated but rather is an important ingredient in the delivery of quality health care. For example, pedicle fixation is the only recognized treatment of certain spinal abnormalities; by taking steps to prevent such treatments, FDA is standing in the way of quality health care delivery. Moreover, FDA clearly lacks the statutory authority to take such steps, since manufacturers that: (1) supply samples of their medical devices for use at educational programs; and (2) supply affiliated medical doctors to demonstrate off-label uses of their devices cannot -- under any stretch of the statutory term -- be said to be engaged in "labeling" activity.

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[7] Since FDA issued the Warning Letters, FDA officials have indicated that the agency is working on yet another limitation on the dissemination of information. Those limits would apply to teaching and training.

In sum, FDA consistently has exceeded its statutory authority in attempting to prevent dissemination of information regarding off-label uses of approved drugs and devices. FDA should withdraw its Draft Policy and issue a new policy that recognizes the important role played by off-label uses of approved drugs and medical devices in the proper administration of health care in this country. The new policy should make clear that FDA will not attempt to interfere with manufacturer distribution of medical textbooks to doctors and will not regulate industry-supported scientific and educational programs other than to ensure they do not include actual labeling activity.

Constitutional Violations. In attempting to suppress discussion of off-label uses of FDA-approved products, FDA is not merely acting in excess of its statutory authority. It is also violating the First Amendment rights of manufacturers and doctors to disseminate truthful information and the First Amendment rights of doctors and patients to receive such information.[8] Petitioners request that FDA cease such First Amendment violations immediately and adopt a policy that makes clear that FDA will hereafter respect First Amendment rights.

To the extent that statements regarding off-label uses constitute noncommercial speech, they are totally off-limits to

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[8] The Supreme Court has made clear that the First Amendment protects both the right of purveyors of information to speak and the right of their audience to receive information. Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council, Inc., 425 U.S. 748, 756 (1976).

FDA regulation.[9] Regulation of noncommercial speech is permissible only under very limited circumstances not present in cases involving discussions of off-label uses of FDA-approved products. Any attempt to prohibit such speech in a noncommercial context would involve regulation based on the content of the speech, and content-based regulation of noncommercial speech is virtually never permissible under the First Amendment. See, e.g., Ward v. Rock Against Racism, 491 U.S. 781, 791 (1989). Much of the speech that FDA is attempting to regulate is noncommercial speech because it is not uttered for the purpose of "proposing a commercial

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[9] For purposes of First Amendment analysis, the U.S. Supreme Court has differentiated between noncommercial and commercial speech. The Court has defined commercial speech as speech that "propose[s] a commercial transaction." Board of Trustees of State Univ. of New York v. Fox, 492 U.S. 469, 109 S. Ct. 3028, 3031 (1989); Central Hudson Gas & Electric Corp. v. Public Service Comm'n of New York, 447 U.S. 557, 562 (1980); Virginia State Board of Pharmacy, 425 U.S. at 762. All other speech is classified as noncommercial speech. Speech that does not propose a commercial transaction does not lose its noncommercial character merely because it is uttered by a corporation (First National Bank of Boston v. Bellotti, 435 U.S. 765 (1978)), or is uttered for a profit. See Fox, 109 S. Ct. at 3036 (providing tutoring services, legal advice, and medical consultation for a fee do not constitute commercial speech because they do not propose a commercial transaction, even though they consist of speech for a profit); Bolger v. Youngs Drug Products Corp., 463 U.S. 60, 67 (1983)("the fact that Youngs has an economic motivation for mailing the pamphlets [discussing use of contraceptives] would clearly be insufficient by itself to turn the material into commercial speech"). While the Supreme Court tolerates somewhat greater government restrictions on commercial speech than on noncommercial speech, the Court has made clear that commercial speech is nonetheless entitled to substantial First Amendment protection. See, e.g., City of Cincinnati v. Discovery Network, Inc., 113 S. Ct. 1505, 1514-16 (1993). The United States Court of Appeals for the Tenth Circuit recently struck down a federal law that prohibited listing alcohol content on beer labeling, on the ground that the statute violated the First Amendment rights of beer manufacturers. Adolph Coors Co. v. Bentsen, ___ F.2d ___ (10th Cir., Aug. 1993).

transaction." Discovery Network, 113 S. Ct. at 1513. While manufacturers may have an economic motivation in disseminating scientific information regarding the usefulness of their products (and/or in subsidizing the efforts of others to disseminate such information), the absence of any explicit or implicit proposition of a commercial transaction takes speech out of the realm of commercial speech and thus out of the realm of virtually all FDA regulation. Id.

But even if one assumes that the speech that FDA is attempting to regulate is commercial speech, FDA's actions still violate First Amendment norms. The government may regulate commercial speech that is neither false nor related to an unlawful activity only upon a showing that: (1) the government has a "substantial" interest that it seeks to achieve; (2) the regulation directly advances the asserted interest; and (3) the regulation is no more extensive than necessary to serve that interest. Central Hudson Gas & Electric Corp. v. Public Services Comm'n of New York, 447 U.S. 557, 566 (1980). FDA's treatment of the off-label use issue suggests that FDA has not even considered the First Amendment implications of its conduct; yet, a brief review of the Central Hudson test strongly suggests that FDA's conduct fails that test.

First, we do not understand FDA to be claiming that off-label use of FDA-approved drugs is illegal; in fact, FDA has repeatedly stated the opposite. Nor have FDA's recent enforcement actions been predicated on the accuracy of the information. Rather, FDA is challenging the information because it discusses an off-label

use. Second, while FDA has a substantial interest in the labeling of drugs and medical devices, its recent regulatory activities do not directly advance that interest because the manufacturer conduct that it has been targeting (such as distribution of medical textbooks to doctors and timely discussion of medical and scientific information in the context of professional meetings before highly knowledgeable audiences) cannot be termed "labeling" under any commonly understood definition of that word.

Finally, even if there were valid public health reasons for attempting to control the activities that FDA has been targeting, FDA's attempts at regulation have been far more extensive than necessary to achieve its purposes. For example, FDA could require that any industry-supported discussion of off-label uses include a warning that FDA has not approved the use being discussed. In the context of audiences consisting of trained medical professionals, such a disclaimer requirement would ensure that FDA-approved drugs and devices are not put to off-label uses without a careful analysis of the pros and cons of doing so. Since FDA's interest in regulating the labeling of drugs and medical devices is fully vindicated by such a disclaimer requirement, FDA's current, far more restrictive regulatory regime cannot pass First Amendment muster under the final prong of the Central Hudson test.

Consequences of FDA's Actions. Petitioner's objections to FDA's conduct are not based on an abstract interest in seeing that First Amendment and statutory norms are adhered to. Rather, Petitioner is filing this Petition because of its belief that FDA's

conduct is interfering with the delivery of effective health care in this country.

The treatment of cancer in children well-illustrates our concerns. Exhibit F is a September 10, 1992 letter to FDA from the Childrens Cancer Group; the letter describes the roadblocks that FDA's policies have placed in the path of treatment of childhood cancers. The incidence of cancer among infants and children is very low in comparison to the incidence of cancer among adults. Accordingly, it is not economically feasible for a company that has developed a cancer drug to undertake the extremely time-consuming and expensive clinical trials necessary to obtain FDA approval for administering the drug to children. As a result, many drugs that reach the market based on demonstrated efficacy against adult cancers never acquire FDA-approved labeling for pediatric use. Nonetheless, such drugs are frequently found by pediatric oncologists to be highly effective against the cancers of children.

But as a result of FDA's restrictions on publicizing off-label uses of FDA-approved drugs, information regarding such findings often is delayed in reaching other physicians who are treating childhood cancers. Such delays are a cause for serious concern, given that the life of children with cancer may hang in the balance. Even though the incidence of cancer in children is low in comparison to cancer in adults, cancer nonetheless is the major medical cause of death from the age of one through adolescence. Moreover, effective treatment of one childhood cancer saves, on average, far more years of life than effective treatment of one

adult cancer.[10] The cure of a child salvages almost an entire lifetime. In light of the urgent need to ensure that pediatric oncologists receive timely information regarding drugs found to be effective in treating childhood cancers, there is no justification for FDA's efforts to prevent the dissemination of that information -- particularly when FDA makes no claim that the information being disseminated (through medical textbooks and through scientific and educational gatherings attended solely by trained professionals) is in any way inaccurate.

D. ENVIRONMENTAL IMPACT

Petitioner claims a categorical exclusion under 21 C.F.R. § 25.24(a)(1).

E. ECONOMIC IMPACT

Petitioner will submit information upon request of the Commissioner. Petitioner believes that the issuance of the Draft Policy in final form -- a policy that curtails and will continue to curtail the availability of accurate medical information -- will raise health care costs and have harmful economic impact on patients and their doctors. Conversely, granting this petition, Petitioner believes, would result in the more effective use of available therapies and therefore have a favorable economic impact.

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[10] The median age at diagnosis of children with cancer is 6, while the median age at diagnosis of adults is 67. The number of children diagnosed with cancer annually in this country places over 300,000 years of potential life at risk.

F. CERTIFICATION

The undersigned certify that, to the best of the knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes all representative data and information known to the Petitioners which are unfavorable to the Petition.

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cc: Commissioner David Kessler
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